ily be exceeded. If prolonged recovery is to be avoided, the larger the initial dose of thiopental that is required, the larger the supplementary doses must be, even in patients of the same size. Patients who require a large initial dose of thiopental will awaken despite plasma concentrations that would normally cause sleep. Although the nature of this acute tolerance is obscure, it is important in its effects on total drug dosage.

Recovery following thiopental should be characterized by smooth, rapid awakening to consciousness. However, if there is postoperative pain, restlessness may become evident and analgesics should be given (an antianalgesic effect of thiopental at low circulating concentrations may be partially responsible). There is often shivering postoperatively as heat is generated to restore body temperature that has decreased during anesthesia and surgery. Postural hypotension may be encountered, and patients should not be moved too hurriedly.

Evaluation. *Disadvantages.* Most of the complications associated with the use of thiopental are minor and can be avoided or minimized by judicious use of the drug. Extravenous or intraarterial injection should be uncommon and, if concentrations no greater than 2.5% are used, are unlikely to cause serious damage. Cough, laryngospasm, and bronchospasm can be serious in certain patients, such as those with elevated intracranial pressure, penetrating injuries of the eye, pharyngeal infections, unstable aneurysms, or asthma. In each such case, adequate anesthesia should be ensured prior to stimulation of the airway.

Overdosage can occur if the specific requirements for each patient are not estimated correctly. There is no effective agent to antagonize the actions of the barbiturates. Hexobarbital and methohexital both cause a higher incidence of motor movements during induction of anesthesia.

The presence of variegate porphyria (South African) or acute intermittent porphyria constitutes an absolute contraindication to the use of barbiturates. In these two forms of porphyria, thiopental or other barbiturates may precipitate a widespread demyelination of peripheral and cranial nerves and disseminated lesions throughout the CNS, resulting in pain, weakness, and paralysis that may be life threatening. Other types of porphyria do not contraindicate the use of barbiturates; this has been a point of confusion.

Advantages. The outstanding advantages of thiopental are rapid, pleasant induction of anesthesia and fast recovery therefrom, with little postanesthetic excitement or vomiting. The use of methohexital is associated with even more rapid recovery of consciousness. These drugs may be given to induce anesthesia prior to administration of another agent, or they can be used alone to provide anesthesia for short procedures that are associated with little pain. They are useful to promote light sleep during regional local anesthesia and for quieting excitement or controlling convulsions.

Status. The ultrashort-acting barbiturates have an important place in the practice of anesthesiology. Thiopental sodium remains the standard for comparison. Thiamylal is very similar; methohexital is more potent and has a somewhat shorter duration of effect. General anesthesia is most often initiated by an injection of thiopental to induce sleep prior to administration of the agents that are necessary for the surgical procedure.

BENZODIAZEPINES

Benzodiazepines were first introduced for the treatment of anxiety, and a large number of these compounds with sedative, antianxiety, anticonvulsant, and muscle relaxant properties have now been synthesized (*see* Chapters 17, 18, 19, and 20). Hypnosis and unconsciousness may be produced with large doses of benzodiazepines, and diazepam, lorazepam, and midazolam have become widely used for preanesthetic medication and to supplement or to induce and maintain anesthesia.

Preparations. *Diazepam* (VALIUM) is insoluble in water and is supplied for injection in a solution of 5 mg of diazepam per milliliter of organic solvents; it should not be diluted. The solution is injected intravenously into the side port of a running intravenous infusion to minimize a burning sensation on injection and the possibility of venous thrombosis. *Lorazepam* (ATIVAN) is supplied at a concentration of 2 or 4 mg/ml of organic solvent for injection; this preparation should be diluted with an equal volume of a compatible solution immediately before intravenous administration. Lorazepam is somewhat less irritating than diazepam, but the same precautions should be observed during injection.

Midazolam (VERSED) is supplied as the hydrochloride at concentrations of 1 and 5 mg/ml. All three drugs can also be given intravenously. Midazolam and lorazepam are about three times more potent than diazepam. Otherwise, their pharmacological properties are similar.

PHARMACOLOGICAL PROPERTIES

Diazepam is discussed as the prototype, and the properties of lorazepam and midazolam are compared where appropriate.

Pharmacokinetics. Following an intravenous injection of 0.1 to 1 mg/kg of diazepam, the drug is rapidly distributed to the brain, but, unlike with thiopental, several minutes pass before the onset of drowsiness. The concentration in plasma declines rapidly owing to redistribution, with an initial half-time of 10 to 15 minutes; however, drowsiness often returns with an increased concentration of diazepam in plasma after 6 to 8 hours. This effect is probably due to absorption from the gastrointestinal tract after excretion in the bile. The onset of drowsiness is slightly less rapid after administration of lorazepam and is slightly more rapid with midazolam; the half-time of redistribution of lorazepam is more than twice that of diazepam. Midazolam and its active metabolite α-hydroxymidazolam are eliminated with half-lives of about 3 hours. Additional information is given in Chapter 17 and Appendix II.

General Anesthetic Action. *Central Nervous System.* The effects of the benzodiazepines on the CNS are described in detail in Chapters 17, 18, 19, and 20. In the doses used to supplement or induce anesthesia, these drugs cause sedation, reduction of anxiety, and amnesia in 50% or more of patients. The amnesia may last up to 6 hours and is characteristically antegrade, with little or no retrograde effect. CNS depression induced by benzodiazepines is partially antagonized by physostigmine (2 mg intravenously), probably owing to inhibition of acetylcholinesterase. If physostigmine is used for this purpose, atropine (1 mg intravenously) should be given to prevent excessive salivation, abdominal cramps, nausea, and vomiting. If the dose of diazepam is very large, the CNS depression may return as physostigmine is eliminated. The administration of aminophylline (1 to 2 mg/kg) can also antagonize CNS depression induced by benzodiazepines. However, both these approaches will probably become obsolete when the specific benzodiazepine antagonist flumazenil is released for general use (White *et al.*, 1989; *see also* Chapter 17).

Circulation and Respiration. By themselves, the benzodiazepines cause only moderate depression of the circulation and respiration. Large doses may cause a 15 to 20% decline in systemic blood pressure and vascular resistance. Changes in heart rate vary from a mild decrease to a moderate increase. If tachycardia occurs, it may compensate for a small decrease in stroke volume and thus limit the modest tendency toward reduction in cardiac output. Stability of the cardiovascular system has encouraged the use of these drugs for anesthesia in patients with cardiac impairment (particularly for diagnostic procedures) (Samuelson *et al.*, 1981). Benzodiazepines are not analgesics, nor can they produce a state of surgical anesthesia when used alone. It is thus necessary to combine several drugs to achieve surgical levels of anesthesia with a balance of sedation, analgesia, amnesia, relaxation, and freedom from reflex stimulation. When opioids are given concurrently with benzodiazepines, the combination may produce severe cardiovascular depression, probably as a result of a sympatholytic action. The same considerations apply to the respiratory effects of benzodiazepines, which are minimal by themselves but in combination with opioids may result in severe and prolonged depression of the respiratory response to hypoxia and to carbon dioxide (Forster *et al.*, 1980; Gross *et al.*, 1983). Transient apnea may follow the rapid injection of diazepam, and facilities for the support of respiration should always be available.

Other Organs. Diazepam neither causes emesis nor prevents it and has little effect on renal, hepatic, or reproductive functions. Although the drug induces relaxation of spastic muscle, which is centrally mediated, it has no effect on the neuromuscular junction and does not enhance or antagonize the actions of specific muscle relaxants. Diazepam crosses the placenta readily and can depress the fetus.

Use in Anesthesia. Diazepam (5 to 10 mg) may be administered orally, intramuscularly, or intravenously for preanesthetic medication about an hour before the patient is transported to the operating area. Benzodiazepines are useful as the sole agent for procedures that do not require analgesia, such as endoscopy, cardioversion, cardiac catheterization, and a spectrum of radiodiagnostic procedures. For induction of anesthesia, the benzodiazepines are given intravenously. However, it is important that the injection be given slowly and that the rate of administration not be so rapid that an excessive dose is given during the period of delayed onset of action. A total dose of 0.6 mg/kg of diazepam administered to an adult will usually result in a sequence of drowsiness, amnesia, and, finally, unconsciousness. Induction with midazolam or lorazepam is similar but requires approximately one third to one half the dose necessary for diazepam. A special application for the benzodiazepines is the control and prevention of seizures induced by local anesthetics during regional techniques. Benzodiazepines are also frequently employed as part of a technique of balanced anesthesia, combined with thiopental for rapid induction, muscle relaxants, analgesics, and, often, an inhalational anesthetic agent. Such a technique has the advantage of requiring a reduced dose of each drug while providing rapid and more precise control of side effects.

Status. The benzodiazepines are useful for their contribution to preanesthetic medication and to induction and maintenance of anesthesia. Midazolam is available as a water-soluble salt, and its in-

place. Potions were also used for sedation and hypnosis, but they were too unpredictable to bequeath to modern medicine. The first agent to be specifically introduced as a sedative and soon thereafter as a hypnotic was bromide (1853, 1864). Only four more sedative-hypnotic drugs (chloral hydrate, paraldehyde, urethane, and sulfonal) were in use before 1900. Barbital was introduced in 1903 and phenobarbital in 1912. Their success spawned the synthesis and testing of over 2500 barbiturates, of which approximately 50 were distributed commercially. The barbiturates held the stage so dominantly that less than a dozen other sedative-hypnotics were successfully marketed before 1960, and several popular old drugs slipped into oblivion.

The partial separation of sedative-hypnotic-anesthetic from anticonvulsant properties, embodied in phenobarbital, led to searches for agents with more selective effects on the functions of the CNS. As a result, relatively nonsedative anticonvulsants, notably phenytoin and trimethadione, were developed in the late 1930s and early 1940s (*see* Chapter 19). The advent of chlorpromazine and meprobamate in the early 1950s, with their taming effects in animals, and the development of increasingly sophisticated methods for evaluating the behavioral effects of drugs set the stage in 1957 for the synthesis of chlordiazepoxide by Sternbach and the discovery of its unique pattern of actions by Randall (*see* Symposium, 1982). With its introduction into clinical medicine in 1961, chlordiazepoxide ushered in the era of benzodiazepines; more than 3000 have been synthesized, over 120 have been tested for biological activity, and about 35 are in clinical use in various parts of the world.

Most of the benzodiazepines that have reached the marketplace were selected for high anxiolytic potential relative to their potency to depress CNS function. Their extraordinary popularity in clinical medicine is due largely to their ability to relieve symptoms of anxiety with relatively little interference with cognitive function or wakefulness. Nevertheless, the benzodiazepines all possess sedative-hypnotic properties to varying degrees; these properties are extensively exploited clinically, especially to facilitate sleep. Mainly because of their remarkably low capacity to produce fatal CNS depression, the benzodiazepines have displaced the barbiturates as sedative-hypnotic agents.

BENZODIAZEPINES

Although the benzodiazepines in clinical use exert qualitatively similar effects, important quantitative differences in their pharmacodynamic spectra and pharmacokinetic properties have led to varying patterns of therapeutic application. There is reason to believe that a number of distinct mechanisms of action contribute in varying degrees to the sedative-hypnotic, muscle relaxant, anxiolytic, and anticonvulsant effects of the benzodiazepines. While only those benzodiazepines used primarily for hypnosis will be discussed in detail, this chapter will describe the general properties of the group and the important differences between individual agents (*see also* Chapters 18 and 19).

Chemistry. The structures of the benzodiazepines in use in the United States are shown in Table 17–1, as are those of a few related compounds to be discussed below.

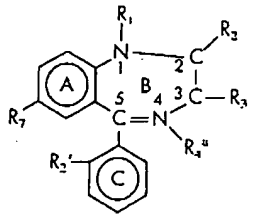
The term *benzodiazepine* refers to the portion of the structure composed of a benzene ring (A) fused to a seven-membered diazepine ring (B). However, since all the important benzodiazepines contain a 5-aryl substituent (ring C) and a 1,4-diazepine ring, the term has come to mean the 5-aryl-1,4-benzodiazepines. Various modifications in the structure of the ring systems have yielded compounds with similar activities. These include 1,5-benzodiazepines (*e.g.*, clobazam) and the replacement of the fused benzene ring (A) with heteroaromatic systems such as thieno (*e.g.*, brotizolam) or pyrazolo (*see* Fryer, in Symposium, 1983a). The 5-aryl substituent greatly enhances potency but can be replaced by a five-membered ring fused to positions 3 and 4 to form an anthramycin.

The chemical nature of substituents at positions 1 to 3 can vary widely and can include triazolo or imidazo rings fused at positions 1 and 2. Electron-withdrawing groups at position 7 markedly enhance activity; electron-releasing or large groups at this position or substituents elsewhere in ring A reduce activity. Electron-withdrawing groups at the 2′ (or ortho) position in ring C enhance potency, while substituents elsewhere decrease activity (*see* Sternbach, in Symposium, 1973). Replacement of ring C with a keto function at position 5 and a methyl substituent at position 4 are important structural features of the benzodiazepine antagonist flumazenil (Ro 15–1788) (*see* Haefely *et al.*, in Symposium, 1983a).

PHARMACOLOGICAL PROPERTIES

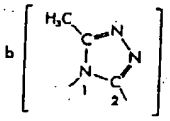
The effects of the benzodiazepines virtually all result from actions of these drugs on the CNS. The most prominent of these effects are sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity. One benzodiazepine, alprazolam, appears to have antidepressant activity in certain clinical settings. Only two effects of these drugs appear to result from actions on peripheral tissues: coronary vasodilatation, seen after intravenous administration of therapeutic doses of certain benzodiazepines, and neu-

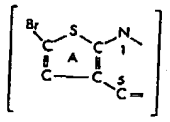
Table 17–1. BENZODIAZEPINES: NAMES AND STRUCTURES *

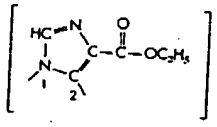


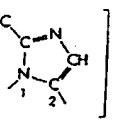
BENZODIAZEPINE	R_1	R_2	R_3	R_7	$R_{2'}$
Alprazolam	[Fused triazolo ring] [b]		—H	—Cl	—H
Brotizolam †	[Fused triazolo ring] [b]		—H	[Thieno ring A] [c]	—Cl
Chlordiazepoxide [a]	(—)	—$NHCH_3$	—H	—Cl	—H
Clobazam [a,†]	—CH_3	=O	—H	—Cl	—H
Clonazepam	—H	=O	—H	—NO_2	—Cl
Clorazepate	—H	=O	—COO^-	—Cl	—H
Demoxepam [a,†,‡]	—H	=O	—H	—Cl	—H
Diazepam	—CH_3	=O	—H	—Cl	—H
Flumazenil [a,†]	[Fused imidazo ring] [d]		—H	—F	[=O at C_5] [e]
Flurazepam	—$CH_2CH_2N(C_2H_5)_2$	=O	—H	—Cl	—F
Halazepam	—CH_2CF_3	=O	—H	—Cl	—H
Lorazepam	—H	=O	—OH	—Cl	—Cl
Midazolam	[Fused imidazo ring] [f]		—H	—Cl	—F
Nitrazepam †	—H	=O	—H	—NO_2	—H
Nordazepam †,§	—H	=O	—H	—Cl	—H
Oxazepam	—H	=O	—OH	—Cl	—H
Prazepam	—CH_2—CH(—CH_2)—CH_2	=O	—H	—Cl	—H
Quazepam†	—CH_2CF_3	=S	—H	—Cl	—F
Temazepam	—CH_3	=O	—OH	—Cl	—H
Triazolam	[Fused triazolo ring] [b]		—H	—Cl	—Cl

* Alphabetical footnotes refer to alterations of the general formula; symbolic footnotes are used for other comments.
† Not available for clinical use in the United States.
‡ Major metabolite of chlordiazepoxide.
§ Major metabolite of diazepam and others; also referred to as nordiazepam and desmethyldiazepam.
* No substituent at position 4, except for chlordiazepoxide and demoxepam, which are N-oxides; R_4 is —CH_3 in flumazenil, in which there is no double bond between positions 4 and 5; R_4 is =O in clobazam, in which position 4 is C and position 5 is N.

b 

c 

d 

f 

[e] No ring C.

romuscular blockade, seen only with very high doses.

Central Nervous System. While the benzodiazepines affect activity at all levels of the neuraxis, some structures are affected to a much greater extent than are others. In addition, some effects of the drugs are indirect. The benzodiazepines are not general neuronal depressants, as are the barbiturates. All the benzodiazepines have very similar pharmacological profiles. Nevertheless, the drugs differ in selectivity, and the clinical usefulness of individual benzodiazepines thus varies considerably.

As the dose of a benzodiazepine is increased, sedation progresses to hypnosis and then to stupor. The clinical literature

often refers to the "anesthetic" effects and uses of certain benzodiazepines, but the drugs do not cause a true general anesthesia, since awareness usually persists and relaxation sufficient to allow surgery cannot be achieved. However, at "preanesthetic" doses, there is amnesia for events subsequent to the administration of the drug; this may create the illusion of previous anesthesia.

The question whether the so-called antianxiety effects of benzodiazepines are the same as or different from the sedative and hypnotic effects has not been resolved. Contributing to this uncertainty are the difficulty in defining and measuring sedation, the difficulty in assessing antianxiety effects in man (*see* Chapter 18), and the unproven validity of various models of anxiety in animals.

The pharmacological profile for a given benzodiazepine varies markedly from species to species. In some species, the subject may become alert before CNS depression is evident. For example, the 7-nitrobenzodiazepines induce hyperactivity in mice, rats, and monkeys, but not in most other species. Interestingly, muscle relaxation in cats and anticonvulsant activity against pentylenetetrazol in mice correlate better with the sedative, antianxiety, and hypnotic properties in man than do the actions to suppress motor activity, induce sleep, and release suppressed behavior in experimental animals.

In animal models of anxiety, most attention has been focused on the ability of benzodiazepines to increase locomotor, feeding, or drinking behavior that has been suppressed by novel or aversive stimuli. For example, animals have been tested in various ways in which behavior that had previously been rewarded by food or water is periodically punished by an electric shock. The time during which shocks are delivered is signaled by some auditory or visual cue, and untreated animals stop performing almost completely when the cue is perceived. The administration of a benzodiazepine can eliminate the difference in behavioral responses during the punished and unpunished periods, usually at doses that do not reduce the rate of unpunished responses or produce other signs of impaired motor function. Similarly, rats placed in an unfamiliar environment exhibit markedly reduced exploratory behavior ("neophobia"), while animals treated with benzodiazepines do not. Opioid analgesics and neuroleptic (antipsychotic) drugs do not increase suppressed behaviors, while phenobarbital and meprobamate usually do so only at doses that also reduce spontaneous or unpunished behaviors or produce ataxia. Descriptions of these and other experimental procedures, as well as discussions of their potential relationship to anxiety in man, can be found in the proceedings of several symposia (*see* Symposium, 1983a, 1983b, 1983c).

The ratio of the dose required to impair motor function to that necessary to increase punished behavior varies widely among the benzodiazepines and depends, not surprisingly, on the species and experimental protocol. While such data may have encouraged the marketing of some benzodiazepines (*e.g.*, flurazepam) only as sedative-hypnotic agents, they have not predicted with any accuracy the relative frequency or intensity of sedative effects among those benzodiazepines marketed as anxiolytic agents (*see* Linnoila, in Symposium, 1983a). To some degree, these discrepancies may have resulted from the fact that observations in animals were often made shortly after parenteral administration, and hence reflected principally the actions of the parent compound. By contrast, after oral administration, a number of benzodiazepines reach the systemic circulation to only a limited extent, if at all, and their effects result primarily from the actions of one or more metabolites (*see* below).

Studies on tolerance in animals are often cited to support the belief that disinhibitory effects of benzodiazepines are separate from their sedative-ataxic effects. For example, tolerance to the depressant effects on rewarded or neutral behavior occurs after several days of treatment with benzodiazepines; the disinhibitory effects of the drugs on punished behavior are augmented initially and decline after 3 to 4 weeks (*see* File, 1985). Although tolerance to the impairment of certain aspects of psychomotor performance (*e.g.*, visual tracking) in man is not usually observed (*see* Linnoila, in Symposium, 1983a), most patients who ingest benzodiazepines chronically report that drowsiness wanes over a few days (*see* Lader and Petursson, in Symposium, 1983c). The development of tolerance to the anxiolytic effects of benzodiazepines is a subject of ongoing debate (Lader and File, 1987). However, most patients maintain themselves on a fairly constant dose; increases or decreases in dosage appear to correspond to changes in problems or stresses. Nevertheless, some patients either do not reduce their dosage when stress is relieved or steadily escalate dosage without apparent reason (*see* Lader and Petursson, in Symposium, 1983c). Such behavior may be associated with the development of drug dependence (*see* Woods *et al.*, 1987).

Some benzodiazepines induce muscle hypotonia without interfering with normal locomotion. They also decrease decerebrate rigidity in cats and rigidity in patients with cerebral palsy. They increase the patellar reflex. In cats, muscle relaxation is effected in doses that are two (flurazepam) to four (clonazepam) orders of magnitude less than those that abolish the righting re-

flex. Diazepam is ten times more selective than meprobamate. However, this remarkable degree of selectivity is not seen in man; clonazepam in nonsedative doses does cause muscle relaxation in man, but diazepam and most other benzodiazepines do not. Tolerance occurs to both the muscle relaxant and ataxic effects of these drugs.

Experimentally, benzodiazepines inhibit seizure activity induced by either pentylenetetrazol or picrotoxin, but strychnine- and maximal electroshock-induced seizures are suppressed only with doses that also severely impair locomotor activity. Flunitrazepam, triazolam, clonazepam, bromazepam, nitrazepam, and nordazepam are more selective anticonvulsants than are other benzodiazepines. Benzodiazepines also suppress photic seizures in baboons and ethanol-withdrawal seizures in man. However, the development of tolerance to the anticonvulsant effects has limited the usefulness of benzodiazepines in the treatment of seizure disorders in man (*see* Chapter 19).

Although analgesic effects of benzodiazepines have been observed in experimental animals, only transient analgesia is apparent in human patients after intravenous administration. Such effects may actually involve the production of amnesia. However, it is clear that benzodiazepines do not cause hyperalgesia, unlike the barbiturates.

Effects on EEG and Sleep Stages. The effects of benzodiazepines on the waking EEG resemble those of other sedative-hypnotic drugs. Alpha activity is decreased, and there is an increase in low-voltage fast activity, especially beta activity. Tolerance occurs to these effects.

Benzodiazepine-induced alterations of the stages of sleep have been studied widely. An excellent compilation of findings and discussion of 66 studies may be found in the review by Kay and associates (1976) (*see also* Greenblatt and Shader, 1974; Mendelson *et al.*, 1977). With a few exceptions, the benzodiazepines are all rather similar in their effects on the important sleep parameters. It is difficult to assess the significance of these exceptions, and they will not be detailed here. Despite the fact that the exceptions are used for promotional purposes, variations in the pharmacokinetic properties of individual benzodiazepines are much more important determinants of the utility of these drugs for their effects on sleep than are differences in their pharmacodynamic properties.

Most benzodiazepines decrease sleep latency, especially when first used, and diminish the number of awakenings and the time spent in stage 0 (a stage of wakefulness). Time in stage 1 (descending drowsiness) is usually decreased, but this is variable. All benzodiazepines increase time spent in stage 2 (which is the major fraction of non–rapid-eye-movement [REM] sleep). Benzodiazepines prominently decrease the time spent in slow-wave sleep (SWS; stages 3 and 4); usually both stages 3 and 4 are shortened. The decrease in stage-4 sleep is accompanied by a reduction in night terrors and nightmares; however, if the decrease is marked, these phenomena may be shifted to the waking hours ("daymares").

Much attention has been paid to the effects on REM sleep. Most benzodiazepines increase REM latency (time from onset of spindle sleep to the first REM burst). The time spent in REM sleep is usually shortened; however, the number of cycles of REM sleep is usually increased, mostly late in the sleep time.

Benzodiazepines do not appear to lessen the relaxation of neck muscles that occurs at the onset of REM sleep. They diminish the frequency of eyeball movement and the magnitude of the bursts of tachycardia that occur during REM sleep and the fluctuations in skin resistance that occur in both stage-2 and REM sleep.

Despite the shortening of stage-4 and REM sleep, the net effect of administration of benzodiazepines is usually an increase in total sleep time. The effect is greatest in subjects with the shortest baseline total sleep time, for whom sleep time may triple. In addition, despite the increase in the number of REM cycles, the number of shifts to lighter sleep stages (1 and 0) and the amount of body movement are diminished. The nocturnal peaks in the concentration of growth hormone in plasma and the concentrations of prolactin and luteinizing hormone are not affected.

Use of benzodiazepines imparts a sense of deep or refreshing sleep, but it is uncertain to which effect on sleep parameters this feeling can be attributed. Some authors have ascribed it to the diminution in REM sleep, but this is not a consistent finding. Others attribute it to the suppression of SWS, but this, too, is inconsistent.

During chronic nocturnal use of benzodiazepines the effects on the various stages of sleep usually decline within a few nights but do not disappear. The number of dreams may double, although dreams usually are less bizarre. If after 3 to 4 weeks of nightly use of a benzodiazepine the drug is discontinued, there may be a considerable rebound in the amount and density of REM sleep. The number of dreams per night is about the same as before the drug was taken, but their bizarre character may increase. There is also usually a rebound in SWS, which may exceed the rebound in REM sleep.

Sites and Mechanisms of CNS Actions. The current predominant view is that most, if not all, of the actions of benzodiazepines are a result of potentiation of the neural inhibition that is mediated by

gamma-aminobutyric acid (GABA). This idea is supported by behavioral and electrophysiological evidence that the effects of benzodiazepines are usually reduced or prevented by prior treatment with antagonists of GABA (*e.g.*, bicuculline) or inhibitors of the synthesis of the transmitter (*e.g.*, thiosemicarbazide). Although possible actions that lead to increased release of GABA cannot be excluded, most attention has been focused on the ability of benzodiazepines to potentiate the actions of GABA on neurons at all levels of the neuraxis. As a result of the detection and characterization of specific binding sites for benzodiazepines, a substantial body of biochemical evidence has accumulated that suggests a close molecular association between sites of action for GABA and the benzodiazepines. The various categories of evidence have been brought together by the discovery that certain congeners of the benzodiazepines are potent and selective inhibitors of both their biological effects and their binding to putative sites of action. One such antagonist (flumazenil) has been investigated extensively for potential clinical use in reversing the effects of high doses of benzodiazepines. Various aspects of the sites and mechanisms of action of the benzodiazepines have been reviewed (*see* Dubnick *et al.*, 1983; Barker *et al.*, 1986; Olsen *et al.*, 1986; Martin, 1987; Gardner, 1988; Polc, 1988) and have been the subject of several symposia (Symposium, 1983a, 1983b, 1983c, 1988a).

Although the GABA-potentiation hypothesis does not yet provide detailed explanations for the therapeutic actions of the benzodiazepines, it does supply a versatile framework with which to connect diverse observations. For example, the remarkable safety of the benzodiazepines can be accounted for by the self-limited nature of neuronal depression that requires the release of an endogenous inhibitory neurotransmitter to be expressed. While barbiturates have similar effects at low doses, they also can mimic the inhibitory actions of GABA at higher doses; thus, they can produce profound depression of the CNS (*see* below). Further, the ability of benzodiazepines to release suppressed behaviors as well as to produce sedation can be ascribed in part to potentiation of GABA-ergic pathways that serve to regulate the firing of neurons containing various monoamines (*see* Chapter 12); these neurons are known to promote behavioral arousal as well as to be important mediators of the inhibitory effects of fear and punishment on behavior. Finally, inhibitory effects on muscular hypertonia or the spread of seizure activity can be rationalized by potentiation of inhibitory GABA-ergic circuits at various levels of the neuraxis. However, a number of observations are not congruent with the exclusive nature of this view, especially those in which the effects of benzodiazepines are not sensitive to antagonists of GABA and/or do not appear to involve changes in chloride conductance (*see* Polc, 1988). Moreover, this hypothesis does not provide an explanation for the ability of relatively low concentrations of antagonists of adenosine receptors (*e.g.*, theophylline) to reverse the neuronal depressant or clinical effects of the benzodiazepines (*see* Phillis and O'Regan, 1988). Despite the impressive array of evidence supporting the GABA-potentiation theory, it does exclude the participation of other mechanisms of action.

In the vast majority of studies conducted *in vivo* or *in situ*, the local or systemic administration of benzodiazepines reduces the spontaneous or evoked electrical activity of major (large) neurons in all regions of the brain and spinal cord; significant effects can usually be detected at doses that are consistent with those used in man. The activity of these neurons is regulated in part by small inhibitory interneurons (predominantly GABA-ergic) arranged in both feedback and feedforward types of circuits (*see* Chapter 12). In the former, axonal branches activate the interneurons, which in turn inhibit the large neuron by way of axosomatic and, sometimes, axodendritic synapses. In feedforward circuits, some or all of the excitatory inputs to the large neuron send collateral axons to inhibitory interneurons that make synaptic contact with the large neuron and/or with excitatory nerve terminals; the latter arrangement is termed *presynaptic inhibition*. The magnitude of the effects produced by benzodiazepines can vary widely and depends upon such factors as the types of inhibitory circuits that are operating, the sources and intensity of ongoing excitatory input, and the manner in which experimental manipulations are performed and assessed. For example, the inhibitory synapses on the neuronal soma, especially those near the axon hillock, are the most powerful and are usually supplied predominantly by recurrent pathways. The synaptic or exogenous application of GABA to this

region can prevent neuronal discharge. This involves a GABA-induced increase in the conductance of chloride, thereby shunting electrical currents that would otherwise depolarize the membrane of the initial segment. Accordingly, benzodiazepines markedly prolong the period that follows brief activation of recurrent GABA-ergic pathways, during which neither spontaneous nor applied excitatory stimuli can evoke neuronal discharge; this effect is reversed by bicuculline.

The effects of the benzodiazepines have also been studied extensively *in vitro*, using brain slices or cultured dissociated neurons. Until quite recently, the concentration of benzodiazepines required to produce GABA-potentiating effects *in vitro* was distressingly high (*e.g.*, 50 to 1000 nM). This can be compared with the concentration of unbound diazepam in the plasma and cerebrospinal fluid (CSF) of patients treated for anxiety (10 to 15 nM) or for status epilepticus (above 35 nM); the latter concentration is usually associated with marked sedation. For unexplained reasons, more recent studies have detected substantial enhancement of GABA-induced chloride currents in cultured neurons using either diazepam or clonazepam at 1 to 10 nM (*see* Macdonald and McLean, 1986). These effects appear to result from an increase in the frequency of bursts of openings of chloride channels induced by submaximal amounts of GABA (Twyman *et al.*, 1989). The benzodiazepines produced no effects on chloride conductances in the absence of GABA.

In other studies, however, these or lower concentrations of benzodiazepines have induced depressant effects on hippocampal pyramidal cells that were insensitive to either bicuculline or picrotoxin (*see* Polc, 1988). These effects have included selective inhibition of cholecystokinin-induced excitation and an enhancement of a Ca^{2+}-dependent K^+ conductance. In both instances, the effects were blocked by benzodiazepine antagonists. At higher concentrations (*e.g.*, 35 to 200 nM clonazepam or diazepam), GABA-independent inhibition of tetrodotoxin-sensitive Na^+ channels has been observed (*see* Macdonald and McLean, 1986). This frequency- and voltage-dependent effect results in reduction of sustained high-frequency, repetitive firing of action potentials, similar to the effects of several antiepileptic agents that are used in the treatment of tonic-clonic seizures (*e.g.*, phenytoin, carbamazepine; *see* Chapter 19). At still higher concentrations (above 1 μM), benzodiazepines can inhibit Ca^{2+} currents and Ca^{2+}-dependent release of neurotransmitters. It is not clear whether such effects involve direct actions of the benzodiazepines or reflect the participation of adenosine (*see* below). There have been no reports on the effect of flumazenil on benzodiazepine-induced inhibitions of Na^+ or Ca^{2+} currents.

Specific binding sites with high (nM) affinity for benzodiazepines have been detected in the CNS of various species, including man; the binding capacity is greatest in the cerebral cortex and least in the spinal cord. The affinity of these sites for benzodiazepines (but not for flumazenil) is enhanced by both GABA and chloride; conversely, benzodiazepines enhance the binding of GABA. The sedative barbiturates increase the binding of both GABA and the benzodiazepines in a chloride-dependent fashion, and these effects are blocked by certain convulsant agents, including picrotoxin (*see* below). These allosteric relationships are retained after solubilization of these receptors with detergent and purification to apparent homogeneity. The isolated macromolecular complex is an oligomer (possibly a tetramer) containing two closely related subunits; photoaffinity labelling experiments indicate that the binding sites for benzodiazepines and GABA-ergic agonists reside on the α and β subunits, respectively (*see* Barnard and Seeburg, in Symposium, 1988a). Recently, complementary DNAs that encode these subunits have been cloned, and RNA derived therefrom has been injected into *Xenopus* oocytes, yielding GABA-regulated chloride channels whose function was enhanced and inhibited by pentobarbital and picrotoxin, respectively. For reasons that have yet to be explained, these maneuvers did not result in the expression of channels that were sensitive to benzodiazepines (Levitan *et al.*, 1988). Thus, the intimate relationship between sites of action for the benzodiazepines and GABA-regulated chloride channels suggested by the biochemical experiments awaits further clarification.

Other evidence for the importance of the high-affinity binding sites in mediating the actions of the benzodiazepines includes a reasonably good correlation between relative binding affinities and relative potencies in producing various effects, especially the release of inhibited behaviors and antagonism of pentylenetetrazol-induced seizures, as long as appropriate adjustments are made for the formation of active metabolites. Most importantly, a number of compounds such as flumazenil compete with active benzodiazepines for such binding sites and antagonize their biological effects. While flumazenil itself is virtually devoid of biological activity, other antagonists display a limited range of benzodiazepine-like properties. The latter group is viewed as "partial agonists" in the classical sense. Still other compounds, many of which are β-carbolines, compete for binding but produce effects that are opposite to those of the benzodiazepines, including inhibition of GABA-induced chloride currents and promotion of seizures. Since their actions are also blocked by flumazenil and other antagonists and go beyond mere reversal of the actions of benzodiazepines, these agents have been called "inverse agonists" (*see* Gardner, 1988).

A number of issues remain unresolved, including an explanation for the different patterns of effects displayed by some of the benzodiazepines currently in clinical use. For example, clonazepam and clobazam produce less sedative-hypnotic effect for a given degree of protection against seizures than other members of the group. One view posits the existence of variant sites of action. Although different types of high-affinity binding sites for benzodiazepines have been detected in the brain, it has not been possible to assign any particular action to a given site. Nevertheless, there is evidence for several different forms of the α subunit of the GABA-

regulated chloride channel, the presumed site of benzodiazepine action (Levitan *et al.*, 1988), and this possibility remains open. Another view ascribes differing patterns of pharmacological effects to the partial agonistic properties of a given agent (*see* Haefely, in Symposium, 1988a). In this view, sedative-hypnotic effects require a relatively high degree of occupancy of sites by a "full" agonist, and the relatively low sedative efficacy of some benzodiazepines (including clonazepam) is attributed to the fact that they are partial agonists. In support of this notion is the growing list of experimental compounds that have a limited ability to enhance the binding and electrophysiological actions of GABA as well as to produce sedation, and that also antagonize the sedative-hypnotic effects of presumed full-agonist benzodiazepines. Still other explanations invoke the participation of sites of action in addition to GABA-regulated chloride channels, especially for effects requiring higher concentrations of the benzodiazepines. As noted above, both Na^+ and Ca^{2+} channels become potential targets at concentrations greater than those associated with anxiolytic or antiepileptic effects. In addition, various benzodiazepines inhibit the uptake of adenosine and potentiate the actions of this endogenous neuronal depressant over this same range of concentrations (*see* Phillis and O'Regan, 1988).

The macromolecular complex containing GABA-regulated chloride channels also appears to be an important site of action of certain steroid anesthetic agents, including alfaxalone, which is in clinical use in Europe, and 3α-hydroxy,5α-dihydroprogesterone, a naturally occurring metabolite of progesterone (Gee *et al.*, 1987, 1988; Harrison *et al.*, 1987). These agents produce barbiturate-like effects, including enhancement of the binding of benzodiazepines and GABA-ergic agonists and promotion of GABA-induced chloride currents. At somewhat higher concentrations, the steroids activate chloride currents in the absence of GABA; this feature also resembles the effects of anesthetic barbiturates. Since glucocorticoids and certain of their metabolites can interact at these sites, it is possible that they may mediate some of the behavioral effects of various steroids.

Respiration. The benzodiazepines have only slight effects on respiration; hypnotic doses are without effect in normal subjects. Preanesthetic doses of diazepam and midazolam slightly depress alveolar ventilation and cause respiratory acidosis as the result of a decrease in hypoxic rather than hypercapnic drive. The rate of expiratory flow is depressed only under hypoxic conditions. In doses used for endoscopy, benzodiazepines decrease alveolar ventilation and P_{O_2}, increase P_{CO_2}, and may cause CO_2 narcosis in patients with chronic obstructive pulmonary disease (*see* Gross *et al.*, 1983; Dundee *et al.*, 1984). Furthermore, diazepam can cause apnea during anesthesia and also when given with opioids. Despite the occasional adverse interaction with opioids, the benzodiazepines do not alter the effect of meperidine on the response to CO_2 (*see* Greenblatt and Shader, 1974). It is noteworthy that in scores of cases of intoxication involving benzodiazepines the only patients who required respiratory assistance were those who had also taken another CNS-depressant drug, especially alcohol (Greenblatt *et al.*, 1977).

Cardiovascular System. The cardiovascular effects of benzodiazepines are minor, except in severe intoxication. In preanesthetic doses, all benzodiazepines decrease blood pressure and increase heart rate. With flunitrazepam and midazolam, the effects are secondary to a decrease in peripheral resistance (Seitz *et al.*, 1977), but with diazepam and lorazepam they are secondary to a decrease in left ventricular work and cardiac output (*see* Rao *et al.*, 1973; Al-Khudhairi *et al.*, 1982). Diazepam increases coronary flow in man (Ikram *et al.*, 1973), possibly by an action to increase interstitial concentrations of adenosine. In large doses, midazolam decreases considerably both cerebral blood flow and oxygen assimilation (Nugent *et al.*, 1982).

Gastrointestinal Tract. Benzodiazepines are thought by some gastroenterologists to improve a variety of "anxiety-related" gastrointestinal disorders. There is a paucity of evidence for direct actions. Benzodiazepines partially protect against stress ulcers in rats, and diazepam markedly decreases nocturnal gastric secretion in man.

Absorption, Fate, and Excretion. The physicochemical and pharmacokinetic properties of the benzodiazepines greatly affect their clinical utility. They all have high lipid:water distribution coefficients in the nonionized form; nevertheless, lipophilicity varies more than 50-fold according to the polarity and electronegativity of various substituents.

All of the benzodiazepines are essentially completely absorbed, with the exception of clorazepate; this drug is rapidly decarboxylated in gastric juice to N-desmethyldiazepam (nordazepam), which is subsequently absorbed completely. Some benzodiazepines (*e.g.*, prazepam and flurazepam) reach the systemic circulation only in the form of active metabolites. After oral administration the time to peak concentration in plasma ranges from 0.5 to 8 hours for the various benzodiazepines. Among those commonly used for their hypnotic effects, peak concentrations of triazolam occur in plasma within 1 hour, while the absorption of temazepam is somewhat slower and more variable. Peak concentrations of active metabolites of flurazepam are attained in 1 to 3 hours. With the exception of lorazepam and midazolam, the absorption of

benzodiazepines tends to be erratic after intramuscular injection.

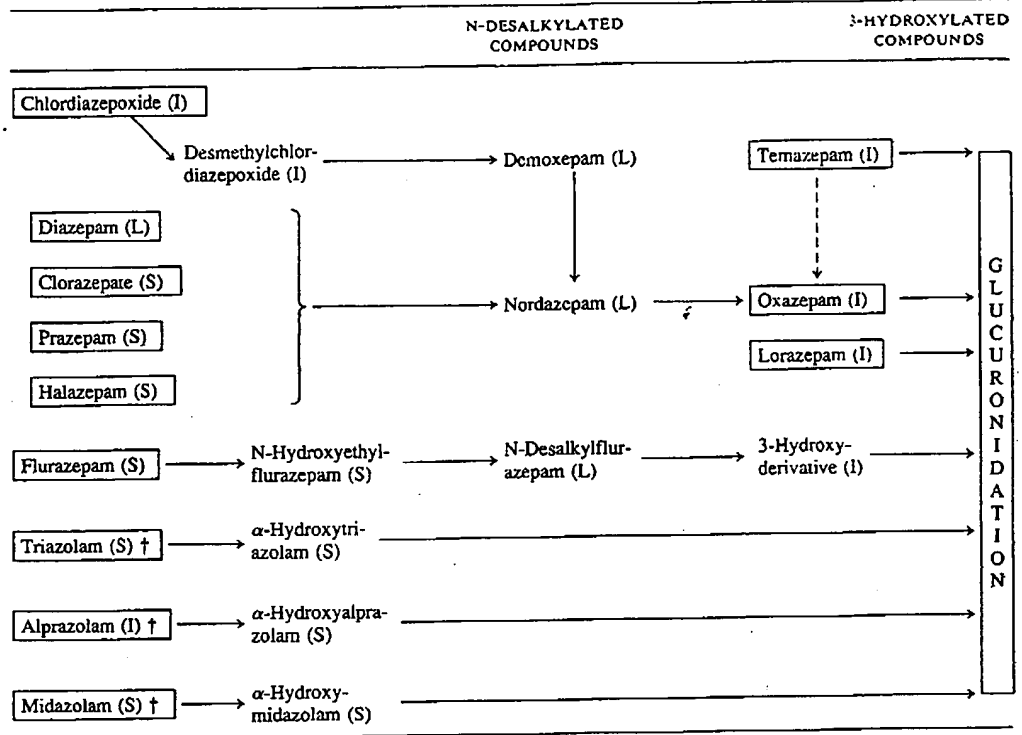
The benzodiazepines and their active metabolites bind to plasma proteins. The extent of binding correlates strongly with lipid solubility and ranges from about 70% for alprazolam to nearly 99% for diazepam. The concentration in the CSF is approximately equal to the concentration of free drug in plasma. While competition with other protein-bound drugs may occur, no clinically significant examples have been reported.

The plasma concentrations of most benzodiazepines exhibit patterns that are consistent with two-compartment models (*see* Chapter 1 and Appendix II), but three-compartment models appear to be more appropriate for the compounds with the highest lipid solubility. Accordingly, there is rapid uptake of benzodiazepines into the brain and other highly perfused organs after intravenous administration (or oral administration of a rapidly absorbed compound); rapid uptake is followed by a phase of redistribution into tissues that are less well perfused, especially muscle and fat. Redistribution is most rapid for drugs with the highest lipid solubility. In the regimens used for nighttime sedation, the rate of redistribution can sometimes have a greater influence than the rate of biotransformation on the duration of CNS effects (Dettli, in Symposium, 1986a). The kinetics of redistribution of diazepam and other lipophilic benzodiazepines is complicated by enterohepatic circulation. The volumes of distribution of the benzodiazepines are large (*see* Appendix II), and many are increased in elderly patients (Swift and Stevenson, in Symposium, 1983a). These drugs cross the placental barrier and are secreted into breast milk.

The benzodiazepines are metabolized extensively, particularly by several different microsomal enzyme systems in the liver. Because active metabolites are generated that are biotransformed more slowly than the parent compound, the duration of action of many benzodiazepines bears little relationship to the half-time of elimination of the drug that has been administered. For example, the half-life of flurazepam in plasma is 2 to 3 hours, but that of a major active metabolite (N-desalkylflurazepam) is 50 hours or more. Conversely, the rate of biotransformation of those agents that are inactivated by the initial reaction is an important determinant of their duration of action; these agents include oxazepam, lorazepam, temazepam, triazolam, and midazolam. Metabolism of the benzodiazepines occurs in three major stages. These and the relationships between the drugs and their metabolites are shown in Table 17–2.

For those benzodiazepines that bear a substituent at position 1 (or 2) of the diazepine ring, the initial and most rapid phase of metabolism involves modification and/or removal of the substituent. With the exception of triazolam, alprazolam, and midazolam, which contain either a fused triazolo or imidazo ring, the eventual products are N-desalkylated compounds; these are all biologically active. One such compound, nordazepam, is a major metabolite common to the biotransformation of diazepam, clorazepate, prazepam, and halazepam; it is also formed from demoxepam, an important metabolite of chlordiazepoxide. The second stage involves hydroxylation at position 3 and also usually yields an active derivative (*e.g.*, oxazepam from nordazepam). The rates of these reactions are usually very much slower than the first stage (half-times greater than 40 to 50 hours), such that appreciable accumulation of hydroxylated products with intact substituents at position 1 does not occur. The accumulation of small amounts of temazepam during the chronic administration of diazepam (not shown in Table 17–2) is an exception to this rule. The third major stage is the conjugation of the 3-hydroxyl compounds, principally with glucuronic acid; the half-times of these reactions are usually between 6 and 12 hours, and the products are invariably inactive. Conjugation is the only major route of metabolism available for oxazepam and lorazepam, and it is the preferred pathway for temazepam because of its slower conversion to oxazepam. Triazolam and alprazolam are metabolized principally by initial hydroxylation of the methyl group on the fused triazolo ring; the absence of a chlorine residue in ring C of alprazolam slows this reaction significantly. The products, sometimes referred to as α-hydroxylated compounds, are quite active but are metabolized very rapidly, primarily by conjugation with glucuronic acid, such that there is no appreciable accumulation of active metabolites. These drugs are also metabolized to a significant extent by hydroxylation at position 3 of the benzodiazepine ring; the rate of this reaction appears to be unusually swift compared with that for compounds without the triazolo ring. These metabolites are rapidly conjugated or oxidized further to benzophenone derivatives, and excreted. Midazolam is metabolized rapidly, primarily by hydroxylation of the methyl group on the fused imidazo ring; only small amounts of 3-hydroxyl compounds are formed (*see* Dundee *et al.*, 1984). The α-hydroxylated com-

Table 17–2. MAJOR METABOLIC RELATIONSHIPS BETWEEN SOME OF THE BENZODIAZEPINES *



* Compounds enclosed in boxes are marketed in the United States. The approximate half-lives of the various compounds are denoted in parentheses: S = <6 hours; I = 6 to 20 hours; L = >20 hours. All compounds except clorazepate are biologically active; the activity of 3-hydroxydesalkylflurazepam has not been determined. Clonazepam (not shown) is an N-desalkyl compound, and it is metabolized primarily by reduction of the 7-NO_2 group to the corresponding amine (inactive), followed by acetylation; its half-life is 20 to 40 hours.

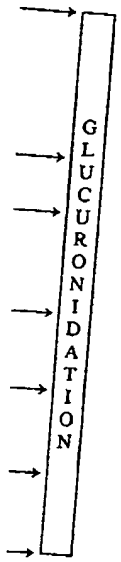
† *See* text for discussion of other pathways of metabolism.

pound, which has appreciable biological activity, is eliminated with a half-time of 1 hour after conjugation with glucuronic acid. Variable and sometimes substantial accumulation of this metabolite has been noted during intravenous infusions (Oldenhof *et al.*, 1988).

The aromatic rings (A and C) of the benzodiazepines are hydroxylated to only a small extent. The only important metabolism at these sites is the reduction of the 7-nitro substituents of clonazepam, nitrazepam, and flunitrazepam; the half-times of these reactions are usually 20 to 40 hours. The resulting amines are inactive and are acetylated to varying degrees before excretion.

Since the benzodiazepines apparently do not significantly induce the synthesis of hepatic microsomal enzymes, their chronic administration usually does not result in the accelerated metabolism of other substances or of the benzodiazepines. Cimetidine and oral contraceptives inhibit N-dealkylation and 3-hydroxylation of benzodiazepines. Ethanol, isoniazid, and phenytoin are less effective in this regard. These reactions are usually reduced to a greater extent in the aged and in patients with chronic liver disease than are those involving conjugation. However, the half-life of temazepam is markedly longer in elderly women compared with young adults or with men of the same age (Smith *et al.*, 1983).

Ideally, a useful hypnotic agent would have a rapid onset of action when taken at bedtime, a sufficiently sustained action to facilitate sleep throughout the night, and no residual action by the following morning. Among those benzodiazepines that are commonly used as hypnotic agents, triazolam theoretically fits this description most closely. Because of the slow rate of elimination of desalkylflurazepam, flurazepam might seem to be unsuitable for this purpose. However, in practice there appear to be some disadvantages to the use of agents that have a relatively rapid rate of disappearance; these disadvantages are not well defined at present but include the phenom-



ena of "rebound" daytime anxiety and early-morning insomnia that are experienced by some patients. With careful selection of dosage, flurazepam and other benzodiazepines with slower rates of elimination than triazolam can be used effectively. The biotransformation and pharmacokinetic properties of the benzodiazepines have been reviewed by Breimer (1979), Bellantuono and associates (1980), Breimer and Jochemsen (in Symposium, 1981), Greenblatt and coworkers (1983a, 1983b, 1983c), and Schütz (1982), as well as in several symposia (Symposium, 1983a, 1983b).

Untoward Effects. At the time of peak concentration in plasma, hypnotic doses of benzodiazepines can be expected to cause varying degrees of lightheadedness, lassitude, increased reaction time, motor incoordination, ataxia, impairment of mental and psychomotor functions, disorganization of thought, confusion, dysarthria, anterograde amnesia, dry mouth, and a bitter taste. Cognition appears to be affected less than motor performance. All of these effects greatly impair driving and other psychomotor skills. When the drug is given at the intended time of sleep, they may not even be noticed, but the persistence of these effects during the waking hours is adverse. Interaction with ethanol may be especially serious. Significant residual effects have been observed after administration of hypnotic doses of a variety of benzodiazepines. For example, in one study the residual effects of two nightly 30-mg doses of flurazepam on driving performance were at least as great as those produced acutely by alcohol at a concentration of 100 mg/dl in blood, a level at which persons usually are considered to be legally intoxicated (*see* O'Hanlon and Volkerts, in Symposium, 1986a). Under the same conditions, significant effects of temazepam (20-mg doses) were not observed. These and other residual effects are clearly dose-related and can be insidious, since most subjects underestimate the degree of their impairment. The intensity and incidence of CNS toxicity generally increase with age; both pharmacokinetic and pharmacodynamic factors are involved (*see* Meyer, 1982; Swift *et al.*, in Symposium, 1983a). The effects of benzodiazepines on performance have been reviewed by Bond and Lader (in Symposium, 1981), by Linnoila (in Symposium, 1983a), and in recent Symposia (1986a, 1986b).

Other relatively common side effects of benzodiazepines are weakness, headache, blurred vision, vertigo, nausea and vomiting, epigastric distress, and diarrhea; joint pains, chest pains, and incontinence may occur in a few recipients. Anticonvulsant benzodiazepines sometimes actually increase the frequency of seizures in patients with epilepsy.

The possible adverse effects of alterations in the sleep pattern will be discussed at the end of this chapter.

Adverse Psychological Effects. Benzodiazepines may cause paradoxical effects. Nitrazepam frequently and flurazepam occasionally increase the incidence of nightmares, especially during the first week of use. Flurazepam occasionally causes garrulousness, anxiety, irritability, tachycardia, and sweating. Euphoria, restlessness, hallucinations, and hypomanic behavior have been reported to occur during use of various benzodiazepines. Antianxiety benzodiazepines have been reported to release bizarre uninhibited behavior in some users with low levels of anxiety; hostility and rage may occur in others. Paranoia, depression, and suicidal ideation occasionally also accompany the use of these agents. However, the incidence of such paradoxical reactions is extremely small (*see* Hall and Zisook, 1981).

Although benzodiazepines have a reputation for causing only a low incidence of abuse and dependence, the possibility of this adverse complication of chronic use must not be overlooked. Mild dependence may develop in many patients who have taken therapeutic doses of benzodiazepines on a regular basis for prolonged periods. Withdrawal symptoms may include temporary intensification of the problems that originally prompted their use (*e.g.*, insomnia, anxiety). Dysphoria, irritability, sweating, unpleasant dreams, tremors, anorexia, and faintness or dizziness may also occur. Hence, it is prudent to taper the dosage gradually when therapy is to be discontinued. During conventional treatment regimens, very few individuals increase their intake without instructions to do so, and

very few manifest compulsive drug-seeking behavior upon discontinuation of a benzodiazepine. It is the patients who have histories of drug or alcohol abuse who are most apt to use these agents inappropriately, and abuse of benzodiazepines usually occurs as part of a pattern of abuse of multiple drugs. In such individuals, benzodiazepines are seldom preferred to barbiturates or even alcohol. The use of high doses of benzodiazepines over prolonged periods can lead to more severe symptoms after discontinuing the drug, including agitation, depression, panic, paranoia, myalgia, muscle twitches, and even convulsions. Dependence on benzodiazepines and their abuse have been reviewed by Marks (1978), Owen and Tyrer (1983), and Woods and colleagues (1987, 1988) as well as in several symposia (Symposium, 1983b, 1983c).

In spite of the adverse effects reviewed above, the benzodiazepines are relatively safe drugs. Even huge doses are rarely fatal unless other drugs are taken concomitantly. Ethanol is a common contributor to deaths involving benzodiazepines, and true coma is uncommon in the absence of another CNS depressant. Although overdosage with a benzodiazepine rarely causes severe cardiovascular or respiratory depression, therapeutic doses can further compromise respiration in patients with chronic obstructive pulmonary disease.

A wide variety of allergic, hepatotoxic, and hematologic reactions to the benzodiazepines may occur, but the incidence is quite low; these reactions have been associated with the use of flurazepam and triazolam, but not with temazepam. Large doses taken just prior to or during labor may cause hypothermia, hypotonia, and mild respiratory depression in the neonate. Abuse by the pregnant mother can result in a withdrawal syndrome in the newborn.

Except for additive effects with other sedative or hypnotic drugs, reports of clinically important, pharmacodynamic interactions between benzodiazepines and other drugs have been infrequent. Ethanol increases both the rate of absorption of benzodiazepines and the associated CNS depression. Valproate and benzodiazepines in combination may cause psychotic episodes. Pharmacokinetic interactions are mentioned above.

THERAPEUTIC USES

The use of the benzodiazepines as hypnotics and sedatives is discussed at the end of this chapter. (*See also* Mitler, 1981; McElnay *et al.*, 1982; Roth *et al.*, 1983.) Other uses of benzodiazepines are as antianxiety agents (Chapter 18), anticonvulsants (Chapter 19), muscle relaxants (Chapter 20), for preanesthetic medication (Chapter 13), and in anesthesia (Chapter 14).

Preparations and Dosage. The aqueous solubility of benzodiazepines ranges from less than 1/10,000 (chlordiazepoxide, lorazepam, oxazepam) to 1/2 (flurazepam hydrochloride). Solubilities in lipid are generally moderate; however, because of the generally low aqueous solubilities, lipid:water partition coefficients are usually high. The official names, trade names, preparations, and sedative and hypnotic doses of these agents are given in Table 17–3.

FLUMAZENIL

Flumazenil, an imidazobenzodiazepine (*see* Table 17–1), is the first specific benzodiazepine antagonist to undergo extensive clinical trial. As noted above, flumazenil binds with high affinity to specific sites, where it competitively antagonizes the binding and allosteric effects of benzodiazepines and other ligands. Both the electrophysiological and behavioral effects of agonist or inverse-agonist benzodiazepines or β-carbolines are also antagonized. In animal studies, the intrinsic pharmacological actions of flumazenil have been quite subtle; effects resembling those of inverse agonists have sometimes been detected at low doses, while slight benzodiazepine-like effects have often been evident at high doses. The underlying mechanisms for such effects are not at all clear; the various hypotheses range from antagonism of endogenous agonist and/or inverse-agonist substances to indirect actions, such as inhibition of adenosine uptake. The evidence for intrinsic activity in human subjects is even more vague, except for modest anticonvulsant effects at high doses.

Upon oral administration, flumazenil is subject to extensive first-pass hepatic metabolism, and less than 20% reaches the systemic circulation. Flumazenil rapidly enters the brain, reaching maximal concentrations within 5 to 10 minutes of injection. The half-time of elimination is somewhat less than 1 hour. Virtually no unchanged flumazenil is excreted in the urine, but little information is available on the nature or activity of metabolites. The brief duration of clinical effects suggests that active metabolites do not accumulate to an appreciable extent.

Flumazenil has been evaluated for its utility in reversing the sedation produced by benzodiazepines administered before or during anesthetic procedures. The intravenous administration of 0.3 to 1 mg of flumazenil is usually sufficient to abolish the effects of therapeutic doses of benzodiazepines within 1 to 2 minutes. There is some debate as to whether the improvement in respiration or consciousness is of significant value when the short-acting midazolam has been used, but its benefits are clear following the use of diazepam. Flumazenil will also awaken patients rendered comatose by the ingestion of excessive doses of benzodiazepines,

Table 17–3. HALF-LIVES, DOSAGE FORMS, AND ORAL DOSAGES OF SEDATIVE-HYPNOTIC DRUGS

DRUG CLASSES, NONPROPRIETARY NAMES, AND TRADE NAMES	HALF-LIFE (*hours*)	DOSAGE FORMS *	ADULT ORAL DOSAGE (*mg*)	
			Sedative †	*Hypnotic*
Benzodiazepines				
Chlordiazepoxide (LIBRIUM, others)	5–15	C,T,I	15–100, 1–3×d ‡	—
Clorazepate (dipotassium) (TRANXENE, others)	50–80 §	C,T	3.75–20, 2–4×d ‡	—
Diazepam (VALIUM, others)	30–60	T,ERC,I,L	5–10, 3–4×d ‡	—
Flurazepam HCl (DALMANE, others)	50–100 §	C	—	15–30
Lorazepam (ATIVAN, others)	10–20	T,I	—	2–4
Oxazepam (SERAX, others)	5–10	C,T	15–30, 3–4×d ‡	—
Temazepam (RESTORIL, others)	10–17	C	—	15–30
Triazolam (HALCION)	2–4	T	—	0.125–0.5
Barbiturates				
Amobarbital (sodium) (AMYTAL)	8–42	C,T,I,P	30–50, 2–3×d	65–200
Aprobarbital (ALURATE)	14–34	E	40, 3×d	40–160
Butabarbital (sodium) (BUTISOL SODIUM, others)	34–42	C,T,E	15–30, 3–4×d	50–100
Butalbital ‖	—	M ‖	—	—
Mephobarbital (MEBARAL)	11–67	T	32–100, 3–4×d	—
Pentobarbital (sodium) (NEMBUTAL)	15–48	C,E,I,S	20, 3–4×d	100
Phenobarbital (sodium) (LUMINAL SODIUM, others)	80–120	C,T,E,I	15–40, 2–3×d	100–320
Secobarbital (sodium) (SECONAL SODIUM)	15–40	C,T,I	30–50, 3–4×d	50–200
Talbutal (LOTUSATE)	—	T	15–40, 2–3×d	120
Miscellaneous				
Chloral hydrate (NOCTEC, others)	4–9.5 §	C,L,S	250, 3×d	500–1000
Ethchlorvynol (PLACIDYL)	10–25 ¶	C	100–200, 2–3×d	500–1000
Ethinamate (VALMID)	—	C	—	500–1000
Glutethimide (DORIDEN, other)	5–22	C,T	—	250–500
Meprobamate (MILTOWN, others)	6–17	ERC,T	400, 3–4×d	—
Methyprylon (NOLUDAR)	3–6	C,T	50–100, 3–4×d	200–400
Paraldehyde (PARAL)	4–10	L,I	2–5 ml, 2–4×d	10–30 ml

* C = capsule; E = elixir; ERC = extended-release capsule; I = injection; L = liquid; P = powder; S = suppository; T = tablet.

† Dose, number per day; dosages do not apply for extended-release forms.

‡ Approved as a sedative-hypnotic drug only for management of alcohol withdrawal; dose in a nontolerant individual would be smaller.

§ Half-life of the active metabolite, to which effects can be attributed.

‖ Marketed only in mixtures.

¶ For acute use, half-life of distribution phase (1–3 hours) may be more appropriate.

even when there is concurrent intoxication with other agents. In general, the administration of 1 to 10 mg of flumazenil intravenously results in a return to consciousness within 5 to 15 minutes, but additional doses may be required after 1 to 2 hours. Flumazenil is not effective in single-drug overdosages with either barbiturates or tricyclic antidepressants; variable or delayed effects have been reported in comatose patients intoxicated with alcohol. The properties and therapeutic uses of flumazenil have been reviewed by Brogden and Goa (1988).

Flumazenil has also been found to diminish the neurological deficits in patients with hepatic encephalopathy (*see* Basile and Gammal, 1988). Hepatic failure is thought to permit the assimilation of benzodiazepine-like substances contained in certain foods or produced by enteric bacteria, or to cause their accumulation in the CSF (Mullen *et al.*, 1988). Although flumazenil has no effect on the course of the underlying hepatic disease, it may prove useful in improving the mental status of patients with hepatic insufficiency.

BARBITURATES

The barbiturates once enjoyed a long period of extensive use as sedative-hypnotic drugs; however, except for a few specialized uses, they have been largely replaced by the much safer benzodiazepines. A more detailed description of the barbiturates can be found in the *fifth edition* of this textbook.

Chemistry. Barbituric acid is 2,4,6-trioxohexahydropyrimidine. The compound lacks central-depressant activity, but the presence of alkyl or aryl groups at position 5 confers sedative-hypnotic and sometimes other activities. The general structural formula for the barbiturates and the structures of those compounds available in the United States are shown in Table 17–4.

The carbonyl group at position 2 takes on acidic character because of lactam ("keto")–lactim ("enol") tautomerization favored by its location between the two electronegative amido nitrogens. The lactim form is favored in alkaline solution, and salts result.

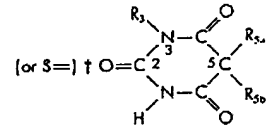
Barbiturates in which the oxygen at C2 is replaced by sulfur are sometimes called thiobarbiturates. These compounds are more lipid-soluble than the corresponding oxybarbiturates. In general, structural changes that increase lipid solubility decrease duration of action, decrease latency to onset of activity, accelerate metabolic degradation, increase binding to albumin, and often increase hypnotic potency.

PHARMACOLOGICAL PROPERTIES

The barbiturates reversibly depress the activity of all excitable tissues. The CNS is exquisitely sensitive, and, even when barbiturates are given in anesthetic concentrations, direct effects on peripheral excitable tissues are weak. However, serious deficits in cardiovascular and other peripheral functions occur in acute barbiturate intoxication.

Table 17–4. BARBITURATES CURRENTLY AVAILABLE IN THE UNITED STATES: NAMES AND STRUCTURES

GENERAL FORMULA:



BARBITURATE	R_{5a}	R_{5b}
Amobarbital	ethyl	isopentyl
Aprobarbital	allyl	isopropyl
Butabarbital	ethyl	*sec*-butyl
Butalbital	allyl	isobutyl
Mephobarbital *	ethyl	phenyl
Metharbital *	ethyl	ethyl
Methohexital *	allyl	1-methyl-2-pentynyl
Pentobarbital	ethyl	1-methylbutyl
Phenobarbital	ethyl	phenyl
Secobarbital	allyl	1-methylbutyl
Talbutal	allyl	*sec*-butyl
Thiamylal †	allyl	1-methylbutyl
Thiopental †	ethyl	1-methylbutyl

* $R_3 = H$, except in mephobarbital, metharbital, and metho- hexital, where it is replaced by CH_3.

† O, except in thiamylal and thiopental, where it is replaced by S.

Central Nervous System. The barbiturates can produce all degrees of depression of the CNS, ranging from mild sedation to general anesthesia. The use of barbiturates for general anesthesia is discussed in Chapter 14. Certain barbiturates, particularly those containing a 5-phenyl substituent (phenobarbital, mephobarbital) have selective anticonvulsant activity (*see* Chapter 19). The antianxiety properties of the barbiturates are not equivalent to those exerted by the benzodiazepines, especially with respect to the degree of sedation that is produced. The barbiturates may have euphoriant effects, which, when maximal, are comparable to those of morphine.

Except for the anticonvulsant activities of phenobarbital and its congeners, the barbiturates possess a low degree of selectivity and therapeutic index. Thus, it is not possible to achieve a desired effect without evidence of general depression of the CNS. Pain perception and reaction are relatively unimpaired until the moment of unconsciousness, and in small doses the barbiturates increase the reaction to painful stimuli. Hence, they cannot be relied upon to produce sedation or sleep in the presence of even moderate pain.

In some individuals and in some circumstances, such as in the presence of pain, barbiturates cause overt excitement instead of sedation. The fact that